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Genetics Behind Uterine Fibroids

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Abstract

Uterine Fibroids is a condition of women specific benign tumor, the clonal neoplasms of smooth muscles with fibroblasts in the uterus. In India uterine fibroids constitute about 37% in rural and 24% in urban population. These fibroids if untreated may become the cause for gynecological disturbances and in some cases fertility issues. Fibroids occur mainly due to the hormonal imbalances in the women during the age of fertility. Apart from its hereditary issues fibroids are regulated by plethora of genes and gene clusters making them a subject of genetic research. The objective of the current review is to identify and study all the genes playing a pivotal role in the development of uterine fibroids. This can be achieved by a crucial data mining protocol along with a focus on mining the gene data bases like NCBI, Gene Cards etc,. Once the list of genes is produced it can be a crucial resource for the genetic annotation of the condition and therapeutic analysis.

***Keywords**:* Uterine Fibroids Hereditary, Benign Tumor, Fertility, NCBI

Introduction

Uterine fibroids as specified are the fibroids/ tumors of the muscular tissue present in the uterus region of the women [7]. They are produced in response to the hormonal disturbances, hereditary or any other life style problem like late pregnancy. They are classified into various types depending on their location in the uterus [4]. Intramural are produced within the muscular wall of he uterus, Submucosal fibroids are those that eject into the uterine cavity, subserosal are present outside the uterine wall. Fig 1 depicts the various types of fibroids with their location.

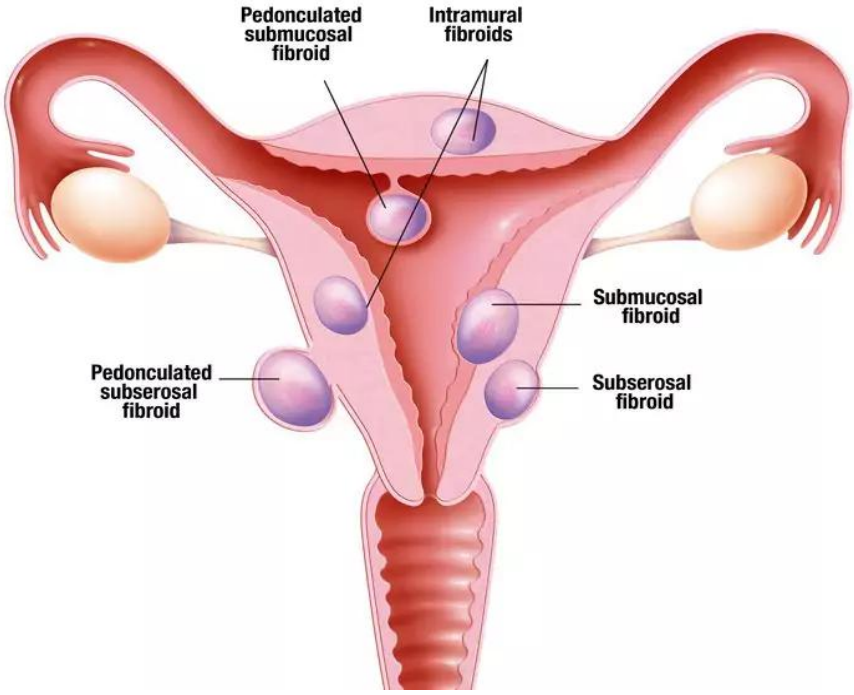
Types of Uterine fibroids

Depending on the location of the tumor within the uterus they are divided into four major types which include

- **Subserosal:** the tumors develop in the outer layer called the serosa of the uterus.
- **Submucosal:** These tumors develop on the internal wall called the mucosa of the uterus.
- **Intramural:** They are developed in the myometrium or within the width of the uterus.
- **Peduculated:** They eject out as a bulb from the uterus and can be considered as a variation of either submucosal or subserosal fibroids.

Among these types the one that projects into the uterine wall, the submucosal type cause major disturbances as they occupy the space which is for the fetal growth, thus hindering the fertility of an individual. In most of the cases these fibroids may not need much concern as they get disintegrated with age and dissolved by themselves without causing any functional disturbance [8]. However in very less no of cases these fibroids may lead to gynecological issues like heavy menstrual bleeding and discomfort or in some cases may be the cause of infertility. Both these conditions demand for a surgical removal or therapeutic dissolution of fibroids.

Figure 1: Structure and types of Uterine Fibroids



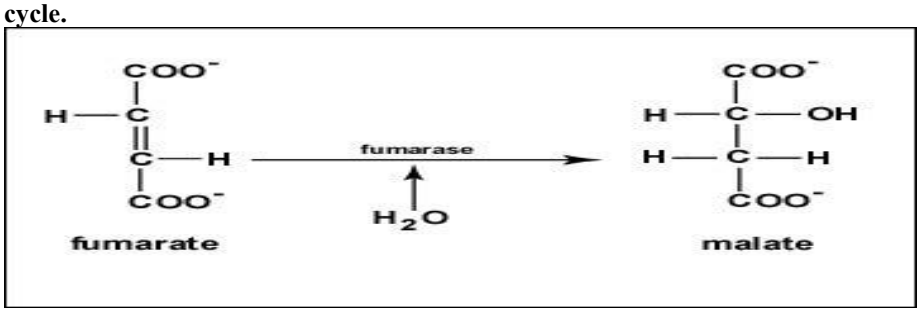
Picture courtesy: National Women's Health Network
The above figure 1 elaborates the different types of fibroids based on their location

Genes involved in Uterine Fibroid development
As stated earlier in the paper there are several vital genes playing their role in the development of fibroids either directly or indirectly. To identify and study these genes NCBI and Gene Cards data base, Research archive Pubmed can be used. Several researchers have studied different genes involved in these leomyomas development. Some of the most vital genes can be studied in the current review.

Though uterine fibroids are known since long, the exact cause of the condition is still unclear. The major cause can be suspected to be the chromosomal aberration especially to the chromosomes 6, 7 12 and 14 [9]. Apart from the chromosomal causes several gene sequence alterations can also be the cause for this condition.

Fumarate Hydratase is one among the vital genes involved in the development of uterine fibroids. Some of the research studies show that the mutations in this gene may stand for the major causes of the condition. The gene is involved in the production of Fumarase a key enzyme in citric acid cycle [13]. It is a vital enzyme involved in the utilization of oxygen by the cell and generation of energy. Any disruption to this gene may lead to hormonal disturbances.

Figure 2 : Equation showing the importance of Fumarate hydratase / Fumarase in Citric acid cycle.



Picture courtesy: Microbiologyinfo.com

Above reaction is a step in citric acid cycle showing the importance of Fumarate Hydratase/Fumarase in the conversion of fumarate to malate.

A research survey was conducted by **Laveta Stewart *et.al***, related to the effect of FH gene mutations on Uterine fibroids [11]. The study included a total of 105 women among which 77 were reported for a prior history of Uterine fibroids. Irrespective of this history 75 of the study population were detected to possess germ line mutations in FH gene. The study revealed a strategic high risk of UF onset among the individuals with a known history of germ line mutations in the gene. Also the women who had prior history of HLRCC (hereditary leiomyomatosis and renal cell cancer) exhibited a high risk for Uterine fibroids indicating the vital role of FH gene.

Niko Välimäki *et.al.* [12], in 2018 conducted an extensive research on the genetic predisposition for uterine fibroids. The study included 15,453 Uterine leiomyoma cases with the number of controls being 392,628. Their study involved the grouping of predisposition genes into two categories: Stability associated genes_ **TERT, TERC, OBFC1** and genes involved in genitourinary development **WNT4, WT1, SALL1, MED12, ESR1, GREB1, FOXO1, DMRT1** and **CD44** antigen. The major finding of the research was the association of germline mutations in MED12 with the onset of Uterine leiomyomas.

Veronica Medikare *et.al.,* in a review article on genetic bases of Uterine fibroids, studied several genes and their importance in uterine fibroids [10]. The authors state the importance of hormones especially estrogens and progesterone as the main promoters of fibroid development. It is also studied that uterine fibroid condition exhibits chromosomal abnormalities. The primary chromosomes involved in the regulation of leiomyomas include chromosome **6, 7, 12 and 14.** Disruption or variation in the two major genes **HMGIC** and **HMGIY** can be the prime causes of fibroid condition. The translocation partners for these genes include **RAD51L1**. Thus several genes and chromosomes involved in the pathogenesis of leiomyomas were detailed
in the article.

Ghada M. A. Ajabnoor et.al., in one of their research studies conducted on the Saudi Arabian women [1] focused on the role of MED12 gene mutations in the development of uterine leiomyomas. According to their research MED12 is a sub unit of mediator complex genes and is known to harbour high degree of mutations. Their work concentrated on identification of various mutations to this gene reflecting the development of uterine fibroids. The study included 308 samples which were subjected for mutation screening. Results indicated that more than 44% of the leiomyomas carried an array of MED 12 mutations in which 30 were missense 1 splice site and 3 indels identified. This study proves the pivotal role played by MED12 and its genetic integrity in the development of uterine leiomyomas.

Pathogenomics of uterine fibroids development was studied by ***Baranov and team*** [2]. Their study involved the identification of molecular meachanisms in the leiomyoma development. Based on the study authors state that there are two major molecular mechanisms involved in the fibroid development. One among the two is the Med12 gene mutations which pose a serious threat in uterine health. Mutations in the leiomyoma stem cells enables the carrying of these fibroid issues to the next generation. Another factor studied is the hypomethylation and epigenic deregulation of HMGA2 which in turn is enhanced by hypoxia, muscle tension etc.

Another research study by **C. S. Gallagher *e.al.***,[5] was about the genome wide association studies and epidemiological analysis of uterine fibroid development. The research was conducted on Europian subjects which included 35,474 cases of Fibroids and 267,505 controls. The study was confined to the genetic association between uterine fibroids and endometriosis. The study identified a significant association between the two conditions with respect to the loci 5p15.33 (TERT), 5q35.2 (FGFR4) and 11q22.3 (ATM). The work also revealed that the victims of endometriosis possess double the changes of developing uterine fibroids. This can be considered as an alarm for the precautions.

Arno E. Commandeur et.al, in their research study on the topic “Epidemiological and genetic clues for molecular mechanisms involved in uterine leiomyoma development and growth” have invested their efforts to understand the genetics behind uterine fibroids [3]. The authors specify in their paper that75% of the women in US have a lifetime risk of developing Uterine fibroids. The author also

specifies that apart from hyterectomy all the other treatment options available are only partial and do not give complete relief from the condition. Several genetic and epidemiological reasons for the condition were screened in the article. The authors present the key role of the two enzymes estrogen and progesterone based on both clinical and experiment data. Results also revealed that the aberrations in the mediator complex subunit 12 (MED12) also play a prominent role in the development of the condition.

Discussion

Uterine fibroid are most prevalent benign, smooth muscle tumors prominent in the women of the fertility age. The leiomyomas exhibit specificity not only in the age and gender but also in the race of the host. Many studies proved the potential high degree of African women being infected than the American or Asian women. This can highlight the role of genetics and environment on the development of these myomas. Apart from the external and hereditary cause there are several individual specific genetic causes for the development of fibroids. Several genes involved in hormonal regulation play a key role in body metabolism and balance. Any disturbance in the sequence, structure or function of these essential genes leads to the condition. Statistically the condition is reported in approximately 40 women for every 100 individuals tested. However the degree is little lowered in urban population when compared to the rural women. 78% of the women in Pakistan are reported to be positive for this condition indicating the high incidence and a need for intense focus. Diagnosis of the condition is usually by scanning performed in response to menstrual or fertility disturbances reported by the victim.

Research studies and case studies revealed the vital role played by genetic factors in the development of Uterine fibroids. Though well studied concept the exact cause of the condition is not clear due to a multitude of reasons in the development of these myomas. The review is focused to identify the various key genes involved ether directly or exhibit an inclined influence on the development of uterine fibroids.

During the study extensive data mining was done using specific databases, especially the PUBMED of NCBI and articles from google scholars related to the genetic basis of utreine fibroids. Among the screened genes the topmost gene identified as a key factor for hormonal regulation and balance was FH Fumarate Hydratase gene. The metabolic function of this gene is to regulate the production of an enzyme fumarase. This enzyme being a key element in the citric acid cycle for the utilization of oxygen and generation of energy. The enzyme is expressed in mitochondrial and cytosolic compartments of the cell. The gene is located on chromosome 9 and any mutations to this gene are known to play a pivotal role in the development of uterine fibroids. Role of FH gene and its mutation on the development of uterine fibroid is well explained in one of our previous research study [6] . There are numerous research studies showing the influence of FH gene mutations in the development of uterine fibroids.

TERT, TERC and OBFC1 are other genes plying an important role in the development of fibroids. These genes are mainly involved in the genome stability whose disturbance causes abnormal conditions. Telomerase reverse transcriptase (TERT), Telomerase RNA complement (TERC) and STN1-CST Complex Subunit (OBFC1) are present on the chromosomes 3, 5 and 10 respectively. Sequence aberrations to these genes leads to the development of fibroids in the uterus.

Other genes include Mediator subunit complex 12 (**Med12)** whose gene variations are highly associated with the development of fibroids. Research also revealed that about 71% of the uterine leiomyomas showed a genetic variation in Med12 Gene emphasizing the importance of Med12 integrity in the prevention of these tumors.

Apart from these specified genes there are several other multiple genes which play a vital role either directly or indirectly in the onset of the fibroids

Conclusion

The above review is a genomic approach for the identification of all possible genes and their role in the development of uterine leiomyomas / fibroids. Further the association of this condition with genomic aberrations. Various researchers across the globe have studied a vast group of genes and their vital role in fibroids. The study concludes to identify some of the common genes to be **Fumarate Hydratase, TERT, TERC, OBFC1, Med 12, WNT4, WT1, SALL1, MED12, ESR1, GREB1, FOXO1, DMRT1** and **CD44** antigen involved in the development of fibroids. Some of the other genes identified in the regulation of condition include HMGIC, HMGIY, RAD 51LI, HMGA2 etc., Important loci involved in the development of this condition include 5p15.33 (TERT), 5q35.2 (FGFR4) and

11q22.3 (ATM). Chromosomal aberrations in the genes 6,7, 12 and 14 also play a major role in the development of Uterine fibroids. These genes can be considered as the targets for disease annotation or therapeutic development.

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